SYNTHESIS OF SOME NOVEL HETEROCYCLIC COMPOUNDS VIA DIPOLAR CYCLOADDITION REACTIONS

Final Synopsis

OF THE Ph.D. THESIS TO BE SUBMITTED TO THE MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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Chapter 1

A BRIEF REVIEW ON THE LITERATURE OF 1, 2, 3 TRIAZOLES.

This chapter deals with the brief review on 1, 2, 3 -triazoles relating to its synthesis, reactions, applications and biological activities based on the publications appeared in the chemical literature.

Five membered heterocycles can be synthesized by using 1, 3 -dipolar cycloaddition reactions[1-6,] which are immensely important class of compounds that occur in a variety of natural products and drugs. The history of 1,3-dipolar cycloaddition goes back to Curtius who discovered the diazoacetic ester in 1883. Later in 1888 his younger colleague Buchner studied the reaction of diazoacetic ester with conjugated esters and this formulated the first example for 1,3 -dipolar cycloaddition reaction. Later, The Huisgen cycloaddition is a reaction that occurs when an organic azide and an alkyne combine in a 1,3-dipolar fashion to produce 1,2,3-triazole. It was first discovered by Rolf Huisgen in the 1960s.The introduction of 1,3-dipolar cycloaddition reactions[7] of substituted organic azide and alkyne has proved to be an efficient and alternate route for the synthesis of 1,2,3-triazole.

The mechanism of the 1,3-dipolar cycloaddition reaction is concerted one with some exceptions where the reaction involves a diradical intermediate. Accordingly there are two mechanisms for 1,3-dipolar cycloaddition reaction, the Huisgen for concerted and Firestone for stepwise mechanism. The mechanism operating in a particular reaction and its regio and stereoselectivity depends on the structure of dipole and dipolarophile involved. 1,3-Dipolar cycloaddition reaction chemistry is associated with enormous advantages such as minimization or elimination of byproduct, higher yield, easy separation, faster reaction rates, economically cheap and environment friendly. This has emerged as an efficient technique for various organic reactions such as, Diels–Alder cycloaddition[8], Robinson's annulation[9], Aldol condensation[10] etc. Due to the wide variety of synthetic applications of 1,3-dipolar cycloaddition reactions, a wide range of dipoles and dipolarophiles were discovered by synthetic chemists till today.

Chalcones are the precursors of flavonoids and isoflavonoids and are found abundant in edible plants. They exhibit variety of pharmacological activities such as anti-inflammatory, antibacterial, anti-tumor, antifungal, antioxidant, immunosuppressive and antinociceptive prop erties[11-20]

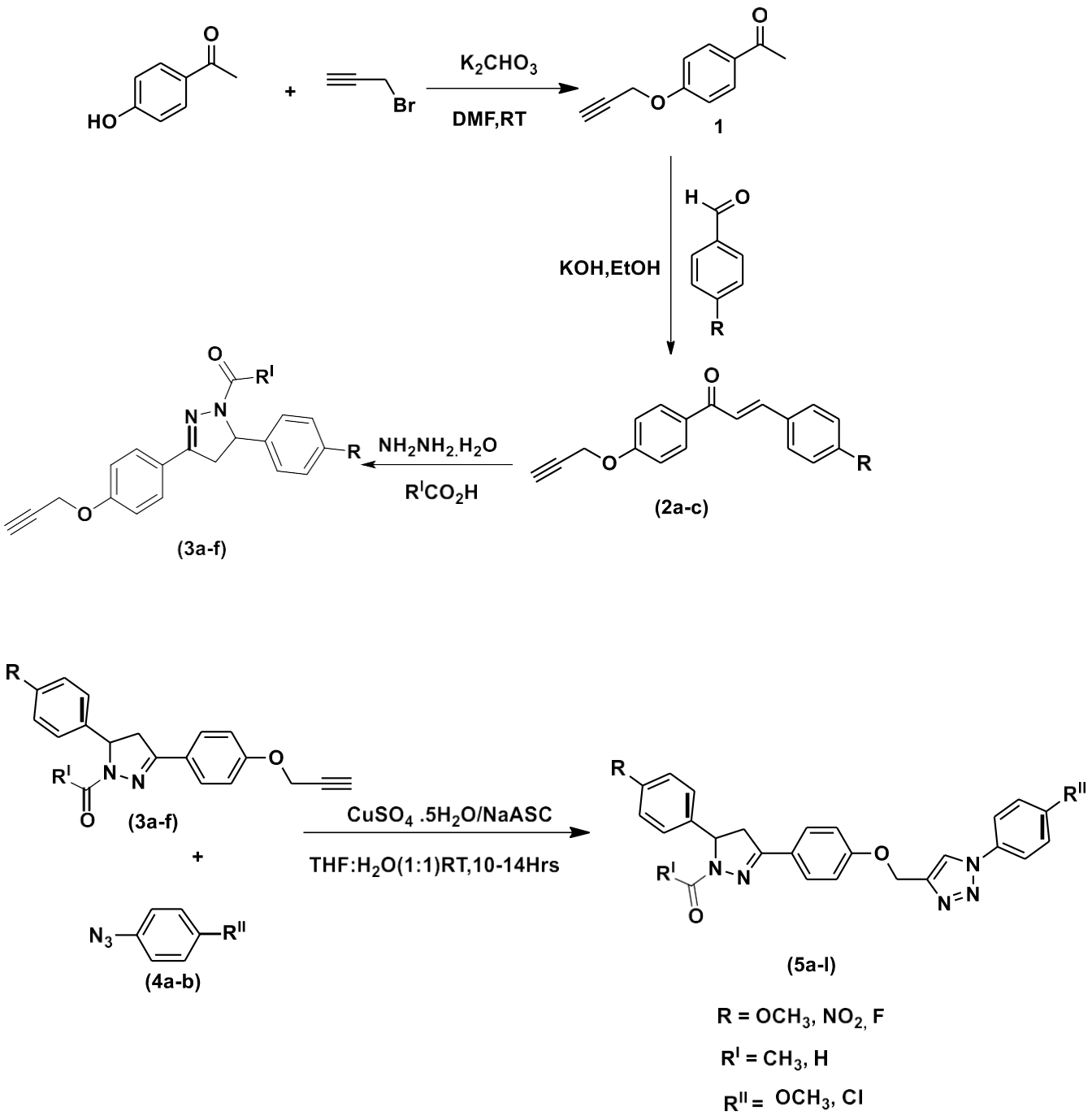
Similarly, pyrazole-based derivatives have shown several pharmacological activities such as antibacterial[21], antifungal, anti-inflammatory[22], antitubercular, anticancer[23], analgesic[24], antipyretic, anticonvulsant[25] etc. In recent years, the synthesis of hybrid heterocyclic molecules which involve the fusion of two biologically active molecules has gained immense popularity[26]. So the present thesis entitled "Synthesis of some novel heterocyclic compounds via dipolar cycloaddition reactions" has been discussed in 5 chapters.

Chapter 2

SYNTHESIS, CHARACTERIZATION ANTIDIABETIC AND ANTIOXIDANT STUDY OF SOME NOVEL PYRAZOLINES CARRYING 1, 2, 3 TRIAZOLE MOIETY

This chapter describes the synthesis of a novel series of 3-(4-((1-(4-substitutedphenyl)-1H-1,2,3-triazol-4-yl)methyleneoxy)phenyl)-4,5-dihydro-5-(3-nitrosphenyl)pyrazole-1-carbaldehyde **(5a-l)** (**Scheme - 2)** by the Cu(II) mediated 1,3-dipolar cycloaddition reactions between 4,5-dihydro-5-(3-nitrophenyl)-3-(4-(prop-2-ynyloxy)phenyl)pyrazole-1-carbaldehyde **(3a-f)** bearing terminal acetylene and 1-azido-4-substitutedbenzene **(4a-b)** The structure of these compounds was confirmed by Infrared (IR), Nuclear Magnetic Resonance (NMR), X-ray Diffraction (XRD), CHN analysis and mass spectral analysis. The compounds were also screened for their antidiabetic and antioxidant activity. The results of these studies are described in this chapter.

The compound 4,5-dihydro-5-(3-nitrophenyl)-3-(4-(prop-2-ynyloxy)phenyl)pyrazole-1-carbaldehyde **(3a-f)** was prepared by the reaction of p-hydroxy acetophenone and propargyl bromide in the presence of potassium carbonate in DMF medium. Obtained 1-(4-(prop-2-yn-1-yloxy)phenyl)ethan-1-one **(1)** was condensed with substituted aldehydes by base catalyzed claisen Schmidt condensation reaction to get 3-(4-methoxyphenyl)-1-(4-(prop-2-ynyloxy)phenyl)prop-2-en-1-one **(2a-c).** Finally the required 4,5-dihydro-5-(3-nitrophenyl)-3-(4-(prop-2-ynyloxy)phenyl)pyrazole-1-carbaldehyde **(3a-f)** were obtained by the reaction with hydrazine hydrate in the presence of different acids. (**Scheme - 2)**


K2CHO3
DMF,RT
1
KOH,EtOH
(2a-c)
NH2NH2.H2O
RICO2H
(3a-f)
CuSO4 .5H2O/NaASC
THF:H2O(1:1)RT,10-14Hrs
(4a-b)
(5a-l)
R = OCH3, NO2, F
RI = CH3, H
RII = OCH3, Cl

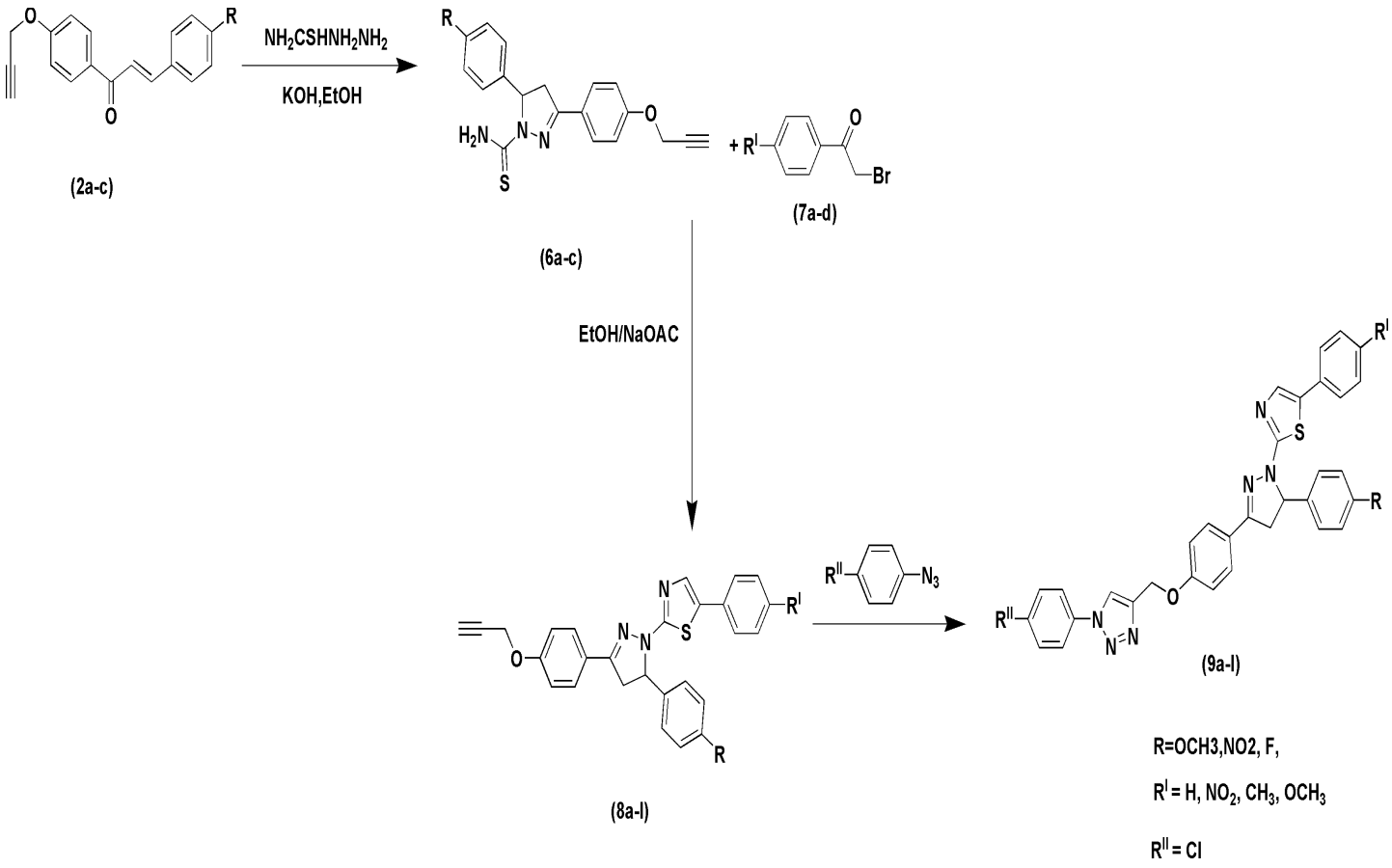
Scheme - 2

Chapter 3

SYNTHESIS, ANTIMICROBIAL, ANTIOXIDANT AND MOLECULAR DOCKING STUDY OF SOME NOVEL 1,2,3-TRIAZOLES CARRYING THIAZOLES AND PYRAZOLINE MOETIES.

This chapter describes the synthesis of a series of novel 2-(3-(4-((1-(p-chlorophenyl)-1H-1,2,3-triazol-4-yl)substituted)phenyl)-5-(p-substitutedphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-phenylthiazole **(9a-l)** (**Scheme - 3)** by the copper catalyzed cycloaddition reaction of 2-(5-(p-methoxyphenyl)-3-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-phenylthiazole **(8a-l)** and p-chloro-azidobenzene. The obtained thiazole intermediate **(8a-l)** was synthesized by the cycloaddition reaction of 5-(p-substitutedphenyl)-3-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide **(6a-c)** with different substituted phenacyl bromides**(7a-d).**

The synthesized 5-(p-substitutedphenyl)-3-(4-(prop-2-yn-1-yloxy)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide **(6a-c)** was prepared from the condensation reaction of chalcones **(2a-c)** with thiosemicarbazide using aqueous ethanol as solvent. These derivatives were screened for their antimicrobial, antioxidant and also molecular docking experiments were carried out. The results of these synthetic, analytical and biological studies form the subject matter of this chapter.



Scheme - 3

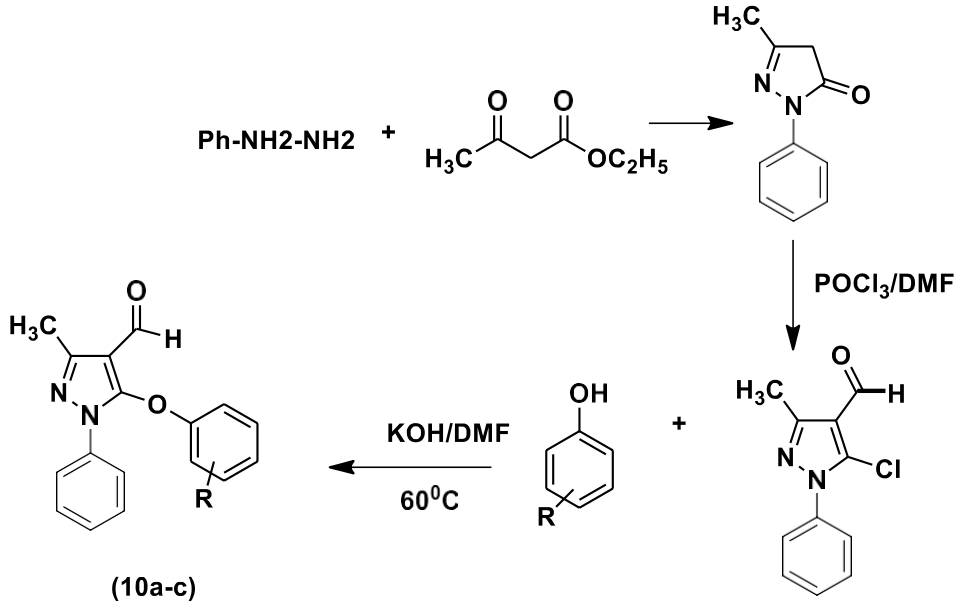
Chapter 4

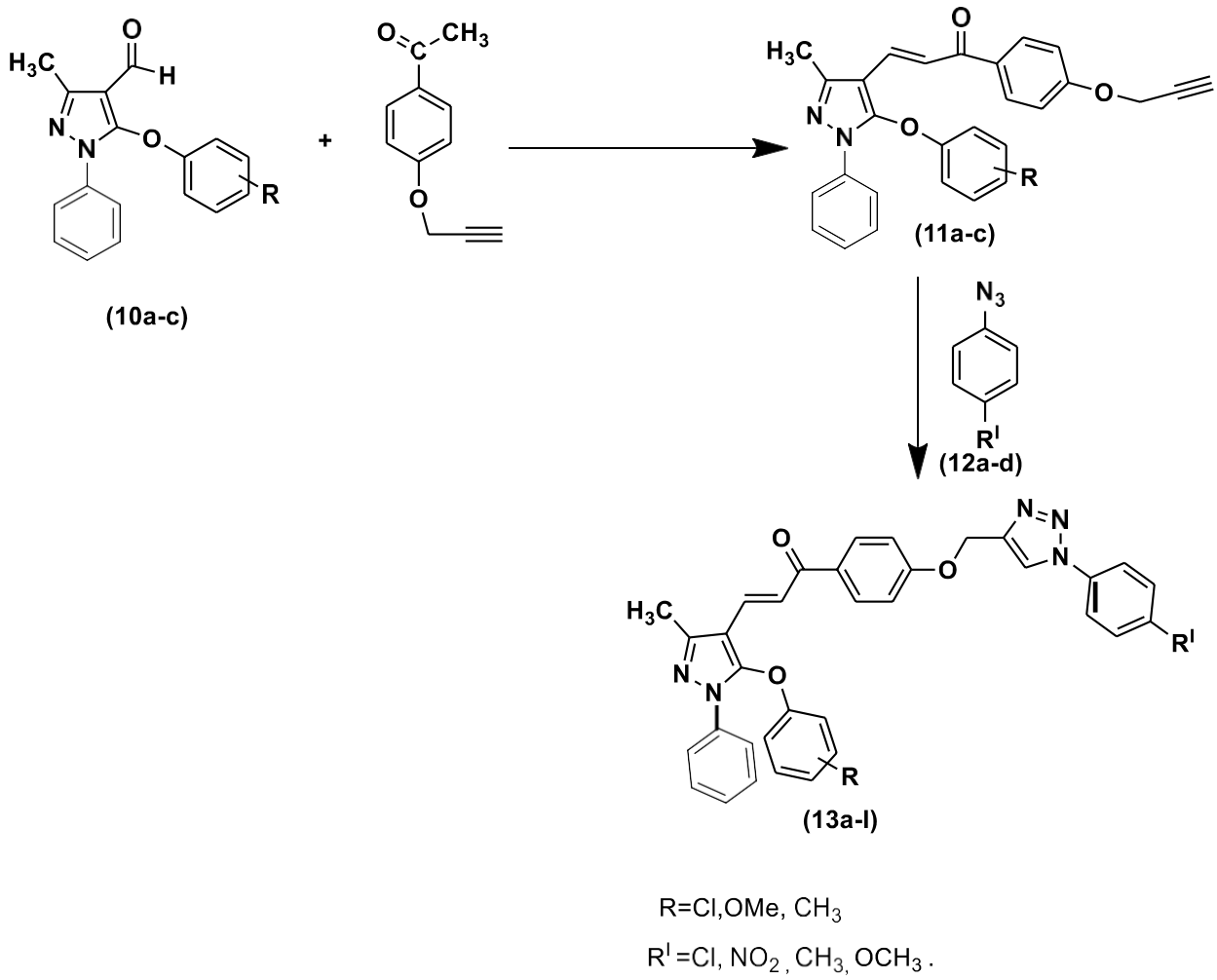
SYNTHESIS, ANTIMICROBIAL, ANTIOXIDANT AND MOLECULAR DOCKING STUDY OF SOME NOVEL 1, 2, 3-TRIAZOLES BEARING PYRAZOLE MOIETY.

This chapter deals with the synthesis, characterization and biological activities of some new 3-(5-(p-sustitutedphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-((1-(p-sustitutedphenyl)-1H-1,2,3-triazol-4-yl)methyleneoxy)phenyl)prop-2-en-1-one **(13a-l).** The compounds **(13a-l)** were synthesized in usual copper catalysed azide-alkyne cycloaddition reaction of substituted azides **(12a-d)** and 3-(5-(4-substitutedphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one **(11a-c)** in a mixture of THF and water in 1:1 ratio. The compounds 3-(5-(4-substitutedphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-(prop-2-yn-1-

yloxy)phenyl)prop-2-en-1-one **(11a-c)** were synthesized by base catalyzed claisen schmidth condensation of 1-(4-(prop-2-ynyloxy)phenyl)ethanone and 5-aryloxy-3-methyl-1-phenyl-1H-pyrazol carbaldehydes (**10a-c**) in ethanol medium.

5- Aryloxy-3-methyl-1-phenyl-1H-pyrazol carbaldehydes (**10a-c**) were prepared by the treatment of phenylhydrazine with ethylacetoacetate followed by Vilsmeier-Haack reaction of pyrazole-5-one to get 5-chloro-3-methyl-1-phenyl-1H-pyrazol carbaldehydes. These carbaldehydes undergo nucleophilic substitution reaction with substituted phenols in presence of KOH in DMSO to give 5-aryloxy-3-methyl-1-phenyl-1H-pyrazol carbaldehydes (**10a-c**) **(Scheme-4).**





Scheme - 4

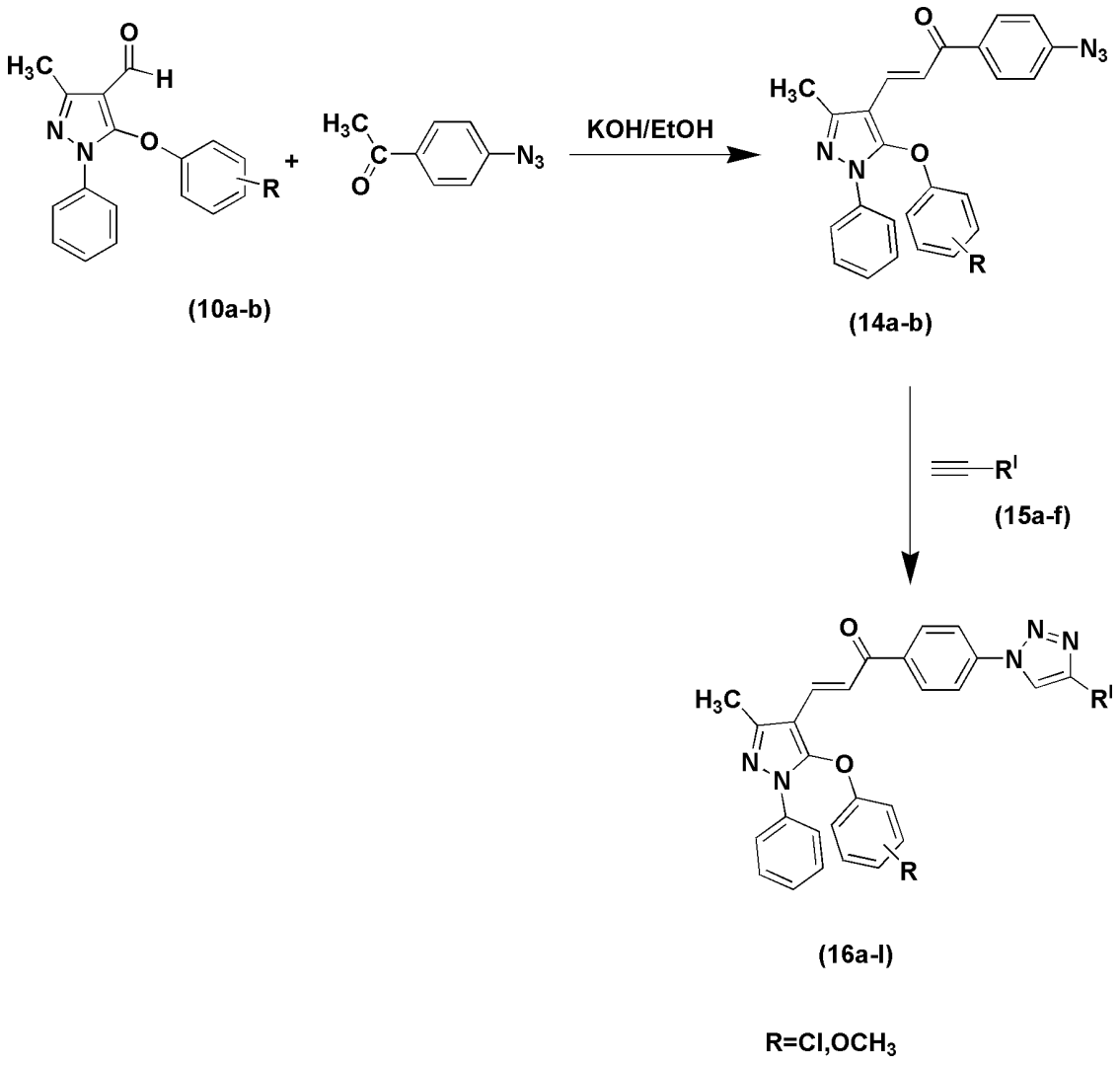
Chapter 5

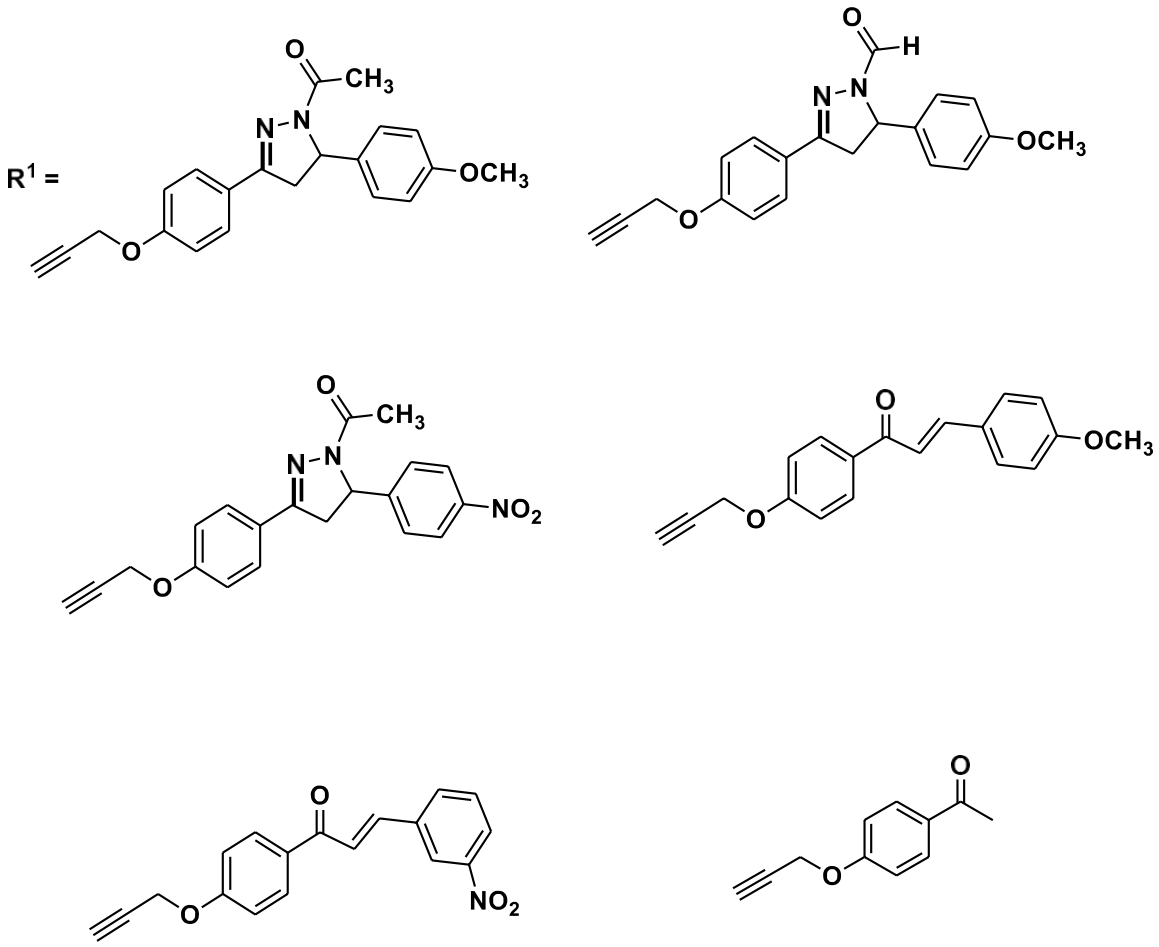
SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDY OF SOME NOVEL 1, 2, 3 TRIAZOLES BEARING CHALCONES AND PYRAZOLE MOIETY.

This chapter describes the synthesis of novel series of 4-(1-((4-(1-acetyl-5-(p-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-3-(5-(4-substitutedphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one **(16a-l)** from various substituted acetylenes **(15a-f)** and 1-(p-azidophenyl)-3-(5-(4-

substitutedphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one**(14a-b)** through the 1,3 dipolar cycloaddition reaction.

1-(p-azidophenyl)-3-(5-(p-substitutedphenoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one**(14a-b)** was synthesized by the base catalyzed condensation reaction of 5-aryloxy-3-methyl-1-phenyl-1H-pyrazol carbaldehydes **(10a-b)** and p-azidoacetophenone in the presence of ethanol medium.





Scheme - 5

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List of research papers published in journals

1. Synthesis of pyrazoline embedded 1,2,3- triazole derivatives via 1,3 dipolar cycloaddition reactions with in vitro and in silico studies" **Nagma Banu H A**, Balakrishna kalluraya, Manju N, Ramith Ramu , Shashank M Patil , Naveen kumar. ,Lokanatha Rai K. M., *ChemistrySelect*, 2023, *8*(13), p.e202203578.
2. "Formation of 1-(thaizol-2-yl)-4,5-dihydropyrazoles from simple precursors:synthesis, spectroscopic characterization and the structures of an intermediate and two products". Ninganayaka Mahesha, Hemmige S. Yathirajan, **Holalagudu A. Nagma Banu**, Balakrishna Kalluraya, Ravindranath S. Rathore and Christopher Glidewell, *Acta Crystallographica section E,*2021.
3. "3-Methyl-5-(4-methylphenoxy)-1-phenyl-1H-pyrazole-4-carbaldehyde"Sreeramapura D. Archana, **Holalagudu A. Nagma Banu**, Balakrishna Kalluraya, Hemmige S. Yathirajan, Rishik Balerao and Ray J. Butcher. IUCrData (2022).

4. "Synthesis and crystal structure of 3-(3-nitrophenyl)-1-(4-(prop-2-ynyloxy)phenyl)prop-2-en-1-one"Vinaya, Yeriyur B. Basavaraju, Hemmige.S. Yathirajan**, Holalagudu A. Nagma Banu,** Balakrishna Kalluraya, Rishik Balerao and Ray J. Butcher. IUCrData(2022).
5. 5-(4-Fluorophenyl)-1-[4-(4-methylphenyl)thiazol-2-yl]-3-[4-(prop-2-yn- yloxy)phenyl]-4,5-dihydro-1H-pyrazole, Archana, S.D.; **Nagma Banu, H.A.;** Kalluraya, B.; Yathirajan, H.S.; Balerao, R.; Butcher, R.J. IUCrData(2022).
6. 5-(4-Methoxyphenyl)-1-[4-(4-methoxyphenyl)thiazol-2-yl]-3-[4-(prop-2-ynyloxy)phenyl]-4,5-dihydro-1H-pyrazole, Sreeramapura D. Archana, **Holalagudu A. Nagma Banu**, Balakrishna Kalluraya, Hemmige S. Yathirajan, Rishik Balerao and Ray J. Butcher, IUCrData(2022).
7. Different patterns of supramolecular aggregation in three amides containing N-(benzo[d]thiazolyl) substituents, Ninganayaka Mahesha, Hemmige S. Yathirajan, **Holalagudu A**. **Nagma Banu**, Balakrishna Kalluraya, Sabine Foro and Christopher Glidewell. *Acta Crystallographica section E,(*2021).

List of research papers presented in conferences

1. "Synthesis of phenanthridine derivatives via electrocyclization of imines under solvothermal Condition". **Nagma Banu H A** and Balakrishna Kalluraya and K M Lokanath rai, poster presentation, International conference of 39th IABMS,15-17th November 2018, Department of Biochemistry, Jnana kaveri P G centre, Mangalore University.

2. "Synthesis and characterization of newly series of 1,3,4-oxadiazol-2-yl-1,2-oxazine derivatives via hetero Diel alder reaction". **Nagma Banu H A** , Balakrishna Kalluraya and K M Lokanath rai, Oral Presentation, 38th annual National conference of Indian council of chemists ,26th to 28th December 2019, organized by department of Chemistry, Jaipur National University, Jaipur. **Received young women researcher award.**

2. "Potassium Iodate (KIO_3) - A Novel Reagent for the dehydrogenation of cyclohexanone" **Nagma Banu H A**, Balakrishna kalluraya, and Lokanatha Rai, Poster presentation, National conference ,17th to 18th october 2019, organized by Department of Material Science and Technology , Vijnana bhavan, Mysore University, Mysore.

3. “Synthesis and characterization of newly series of oxazine derivatives via hetero Diel alder reaction”. **Nagma Banu H A** , Balakrishna Kalluraya and K M Lokanath rai,National Conference, 12th febraury 2020.department of chemistry, FMKMC madikeri, secured first place in poster presentation.
4. “Synthesis of hybrid molecules containing nitrogen heterocycles and their antimicrobial activity”. **Nagma Banu H A** , Balakrishna Kalluraya and K M Lokanath rai, National conference, NCCCAIAM-2021,26th March 2021, Department of Chemistry, Govindadas college, Surathkal.
5. “Synthesis and characterization of newly series of N-heterocyclic derivatives via 1,3 dipolar cycloaddition reaction”. **Nagma Banu H A** , Balakrishna Kalluraya and K M Lokanath rai, National Conference, 5th febraury 2019.department of chemistry, FMKMC madikeri, secured first place in poster presentation.
6. “Synthesis of hybrid molecules containing nitrogen heterocycles and their antimicrobial activity”. **Nagma Banu H A** , Balakrishna Kalluraya and K M Lokanath rai, Virtual conference, poster presentation, JNOST-16, October 31-November 1st 2020. IISC Bangalore,in collaboration with Germany University.
7. "Synthesis of fused pyrazole and thiazole derivatives as antimicrobial candidates withmo lecular docking studies", **Nagma Banu H A** and Balakrishna Kalluraya Oral presentation. International conference 2022, 3rd and 4th August,2022. Department of Chemistry, Srinivas institute of technology, Mangalore.

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